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THE TOTAL SYNTHESES OF (±)-α- AND β-DIHYDROCLEAVAMINES, (±)-16-METHOXYCARBONYLDIHYDROCLEAVAMINE, (±)-CORONARIDINE, (±)-DIHYDROCATHARANTHINE, (±)-IBOGAMINE, (±)-EPI-IBOGAMINE AND (±)-CATHARANTHINE†

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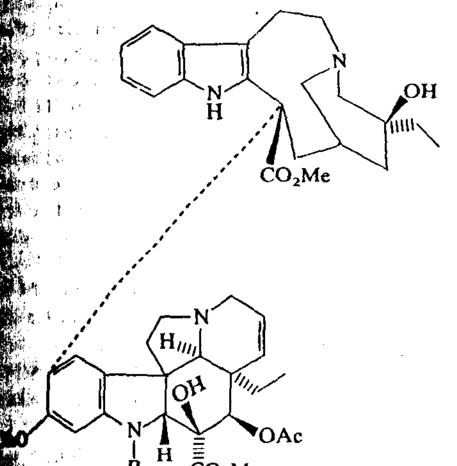
Abstract—The total syntheses of (±)α- and β-dihydrocleavamines, (±)-16-methoxycarbonyldihydrocleavamine, (±)-coronaridine, (±)-dihydrocatharanthine, (±)-ibogamine, (±)-epi-ibogamine and (±)-catharanthine are described.

binary anti-tumor alkaloids vinblastine (1) and ine (2) comprise a tetracyclic indole moiety to a pentacyclic dihydroinole moiety.[1,2] The indole moiety in vinblastine is the *Aspidos*- alkaloid vindoline, a major alkaloidal con- of the leaves of *Catharanthus roseus*. The moiety of vinblastine contains a novel 9-ered nitrogen containing ring, and it does not separately in these plants.[3] Metal-acid cleav- of vinblastine and other related binary al- gives rise to the dihydrocleavamines formed avage and disproportionation reactions.[4] At- was therefore first directed at developing a is of α- and β-dihydrocleavamines.

scheme adopted for the synthesis of α- and drocleavamines is shown in Scheme 1. l-α-ethyl acrylate (4) was prepared by a slight ation of the method described by Japanese ers.[5] Mannich had also prepared this compound by a similar route.[6] The reaction involved is essentially a Mannich reaction of the half ester of dimethyl-2-ethylmalonate with diethylamine and formaldehyde. The product was obtainable in 80% yield from dimethylmalonate. This was converted to ethyl 2-carbethoxy-4, 4-diethoxy butanoate (3) which had been previously prepared[7] by an autoclave reaction between the sodio derivative of diethyl malonate and bromoacetal. As this preparation procedure of the compounds 3 is rather cumbersome, the procedure was modified by refluxing suitable quantities of sodiodiethyl malonate and bromoacetal with dimethylformamide and sufficient ethanol to maintain the reflux temperature of the azeotropic mixture at 120° for 4 hr. A yield of over 70% of the product 3 could thus be obtained.


(1): $R = CH_3$
(2): $R = CHO$

A Michael addition of ethyl 2-carbethoxy-4, 4-diethoxy butanoate (3) with methyl-α-ethyl acrylate proved initially to be a poor reaction (25-30% yields). After manipulation of experimental conditions, it was found possible to obtain yields of up to 86% of 5 when an approximate 0.5 molar excess of α-ethyl acrylate was present with freshly prepared sodium ethoxide used as the catalyst. The initial difficulties in obtaining good yields in this Michael addition were in contrast to the ease with which methyl acrylate itself was found to undergo Michael addition with dimethylmalonate. It appears that the presence of an Et side chain in the accepter molecule slows down the rate of addition and thereby aids the retro-Michael reaction. The difficulty encountered in Michael additions due to the presence of substituents at the α,β-double bond of the accepter molecule is well known.[8]

Methyl-2-ethyl-4, 4-dicarbethoxy-6, 6-diethoxy hexanoate (5) obtained as a colourless viscous liquid from the Michael addition, was then refluxed with recrystallised tryptamine in aqueous acetic acid to afford the diester 7 as a pale brown gum. Tlc and spectroscopy of this and subsequent synthetic intermediates established that they were a mixture of the various possible diastereoisomers with no stereoselectivity being observed during the reaction. The diester 7 was hydrolysed in refluxing

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aqueous methanolic potassium hydroxide to the corresponding diacid **8.** It was found that when the amorphous solid was triturated with a limited amount of chloroform, the impurities tended to dissolve preferentially leaving a white crystalline material (m.p. 173–174°) behind.

An alternative synthesis of the diester **7** attempted was to condense ethyl-2-carbethoxy-4, 4-diethoxybutanoate (**3**) directly with tryptamine in the presence of aqueous acetic acid. This afforded the corresponding indolic amide ester which crystallised from ethanol as white crystalline needles. Several attempts were made to effect the Michael addition of this substance with methyl-α-ethylacrylate but only unreacted starting material was obtained.

Pyrolytic decarboxylation of the diacid **8** under vacuum resulted in the formation of the monoacid **9** in 50% yield which crystallized from aqueous methanol (m.p. 219–222°). A substantial increase in yield to 80% in the pyrolytic decaroxylation reaction was achieved if the starting diacid **8** was intimately ground with copper-bronze powder and the mixture pyrolysed under vacuum.

Esterification of the monoacid **9** by refluxing it in anhydrous methanol and boron trifluoride-methanol complex afforded ester **10** in excellent yields. This crystallized readily from benzene, (m.pt. 71°). This important intermediate was subsequently also employed in the synthesis of 16-hydroxydihydrocleavamine and 16-epideoxydemethoxycarbonylvinblastine.

An alternative shorter route to the synthesis of the ester **10** was developed[9] after the original synthesis of dihydrocleavamine was complete.[10] Krapcho *et al* had published[11] a novel synthetic procedure for the conversion of geminal diesters to the corresponding mono-esters by allowing the diesters to react with sodium cyanide in dimethyl sulphoxide at about 160° for 4 hr. As the classical procedure involving hydrolysis to the diacid, decarboxylation to the corresponding monoacid and esterification resulted in lower overall yields, it was decided to attempt a similar decarbethoxylation on the geminal diester **5.** The ester when refluxed with 1.5 equivalents of dry sodium cyanide in dry dimethyl sulphoxide gave a pale yellow lower boiling liquid **6** in 70% yield. This was condensed directly with tryptamine in refluxing aqueous acetic acid to give a crystalline compound in 85% yield on work-up which was found to be identical with the lactam ester **10.** This method thus provided a shorter and more elegant route to this valuable intermediate.

The lactam ester **10** was reduced with LAH in refluxing anhydrous tetrahydrofuran to the amine alcohol **11.** Initial attempts at tosylation of the alcohol **11** with *p*-toluenesulphonyl chloride in pyridine did not prove successful. However mesylation with anhydrous methane sulphonyl chloride and trimethylamine in anhydrous ether resulted in an immediate precipitation of a pale yellow solid which was found to be a mixture of the hydrochlorides of the mesylate and the amine alcohol. The product was refluxed for several hours in anhydrous acetonitrile until tlc showed complete conversion of the mesylate to the corresponding quatern **12.** The unreacted amine alcohol **11** could b vered from the organic extracts and recycl the original mesylation reaction.

The crucial reactions of the synthesis inv reductive cleavage of the pentacyclic qu salt **12** to dihydrocleavamine. Similar red had been reported in the literature.[12,13] A nation of the structure of the quaternary shows that cleavage of four C–$N_{(b)}$ bon theoretically possible. The most favourable age, however, would be between $N_{(b)}$ and since the radical intermediate would be sta by delocalisation over the indole nucleus. This lization is not possible in any of the alter cleavages.

Reduction of the quaternary salt with so and liquid ammonia afforded a colourless sub which moved as two spots on tlc. On separati preparative tlc the two compounds obtained w found to be identical (tlc, mass spectrometry, etc) to authentic samples of α- and dihydrocleavamines.† High resolution mass trometry on the molecular ion, *m/e* 282, conf the molecular formula to be $C_{19}H_{26}N_2$.

Alternative reductions of the quaternary sa to α-and β-dihydrocleavamines were carried with LAH in N-methylmorpholine or lithi liquid ammonia but the best yields (over were obtained when sodium and liquid am were used as the reducing medium.

The overall yield of dihydrocleavamine ob ble starting from the aliphatic acetal diester **6** as high as 60%. Since the acetal diester **6** is re obtainable by the decarbothoxylation of the tr **5,** this synthesis constitutes a short and high procedure for preparing α- and β-di cleavamines.

The announcement of the synthesis of α-an dihydrocleavamines[10] was followed by the pub tion by Kutney *et al.* at the University of B Columbia of the syntheses of these compound well as 16-methoxycarbonyldihydrocleavam Interestingly the last few intermediates prepared Kutney, namely the amine alcohol and the qu nary salt, are identical with compounds **11** and prepared by us. However, a comparatively lo approach has been adopted by the Canadian In particular a low yield mercuric acetate oxid was used which gave a complex mixture of products in 42% yield, only one of which was desired intermediate. The synthesis of dihy leavamine described here provides the first and high yield route to the skeleton of the ind moiety of vinblastine.

Attention was next directed towards develo a general synthetic route to the *Iboga* alka such as ibogamine **15** and coronaridine **19** w possess a pentacyclic skeleton consisting of an dole nucleus fused to a cage-like isoquinucli ring system. Since 16-methoxycarbonyldihy cleavamine (**18**) is known[15] to be convertible to

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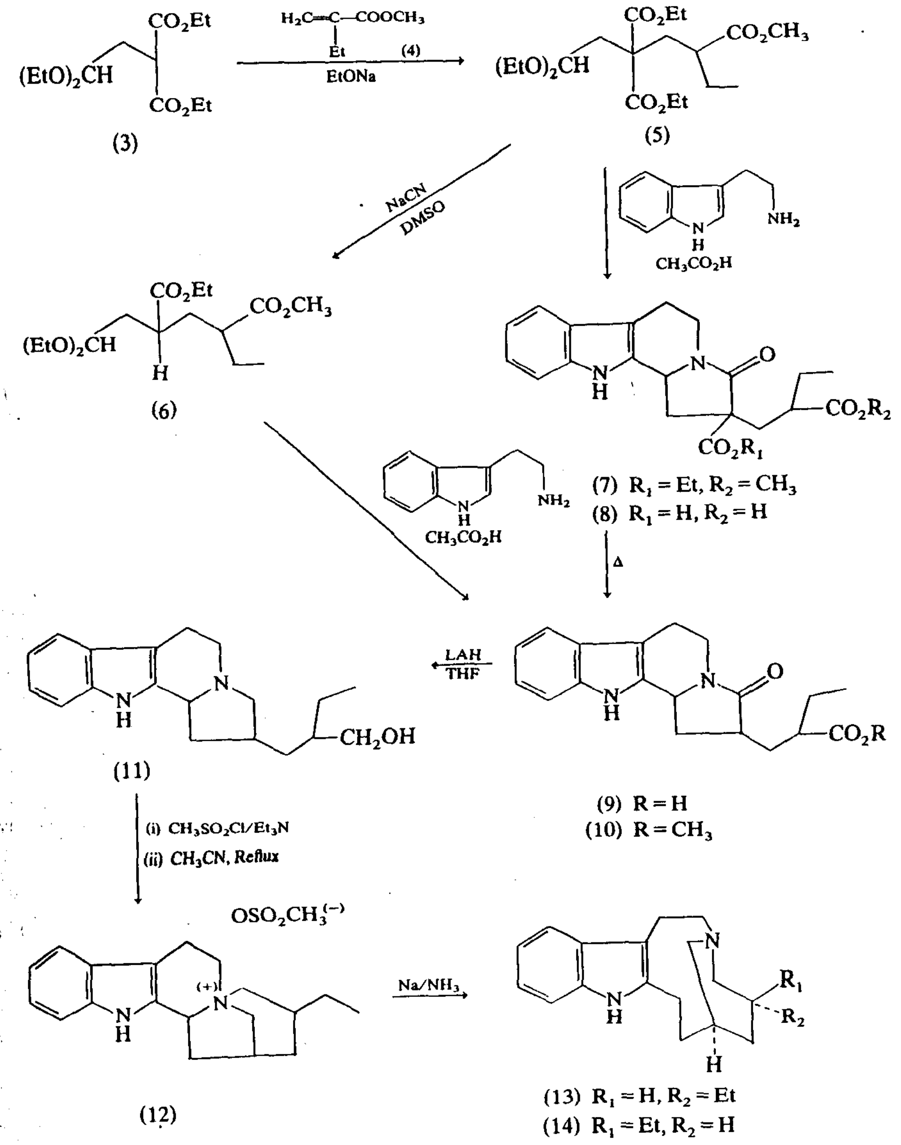
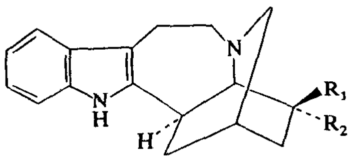
† Kindly supplied by Dr. N. Neuss of Ely Lilly & Indianapolis, U.S.A.



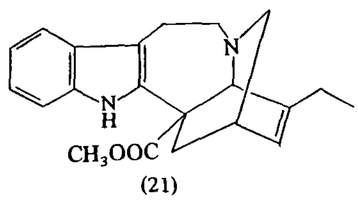
ious *Iboga* alkaloids, it was of interest to establish a synthetic route to this substance. It was hoped that if cyanide anion was allowed to attack the quaternary salt (**12**), attack at C-16 might occur preferentially with the concurrent cleavage of the C—N† bond to afford the 16-cyano compound **4** directly. Kutney had earlier affected a synthesis of (±)-16-methoxycarbonyldihydrocleavamine[14] by attack of cyanide on the chloroindolenine of dihydrocleavamine[16] followed by hydrolysis and esterification, but found the reaction to proceed in very low yields.‡ Moreover since the synthesis of dihydrocleavamine itself as affected by Kutney[16] was such a low yield process, it did not provide a satisfactory route to 16-methoxycarbonyl dihydrocleavamine (**18**). It was desirable therefore to develop a route to **18** from the quaternary salt **12**,



(1)

(15): $R_1 = Et, R_2 = H$,

(16): $R_1 = H, R_2 = Et$,



(21)

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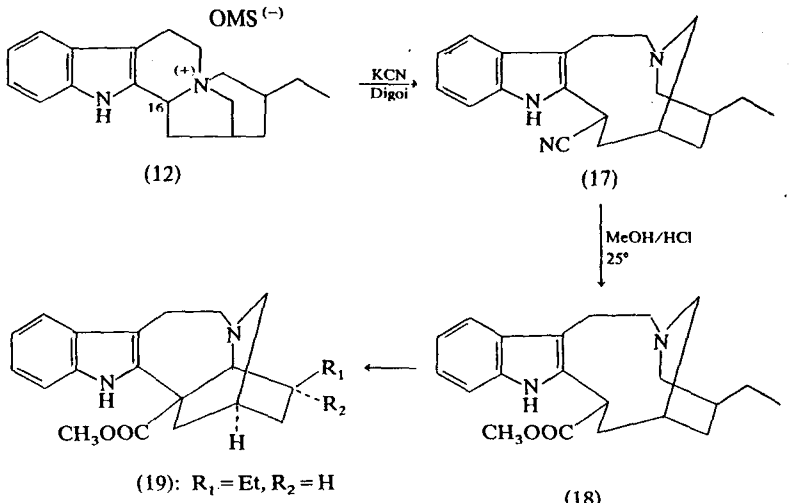
† The chloroindolenine procedure for attack of nucleophiles at C-16 was originally developed by Buchi[28] and later applied by Kutney and us.

‡ They have subsequently reverted to our original method for the synthesis of this compound by obtaining a quaternary salt 3, by the quaternization of dihydrocleavamine chloroindolenine and cleaving the C—N bond with potassium cyanide in DMF.[19]



(12)

(17)

(18)

(19): $R_1 = Et, R_2 = H$
(20): $R_1 = H, R_2 = Et$

which is obtainable in high yields and thence to the *Iboga* alkaloids coronaridine (19), dihydrocatharanthine (20), ibogamine (15), epi-ibogamine (16), and catharanthine (21).

When the salt **12** was heated at 200° with KCN in digol, appreciable decomposition was found to occur. It was found possible, however, to isolate a crystalline indolic compound from the dark brown gum in low yields. The IR spectrum showed the presence of C≡N vibrations at 2240 cm^{-1}, and "Bohlmann bands" at 2805 cm^{-1} and 2755 cm^{-1} characteristic of those structures in which the nitrogen (N_b) lone pair of electrons is transcoplanar with at least two H atoms on the α-carbon. The mass spectrum of the cyano compound showed the presence of the molecular ion at *m/e* 340 and the predicted fragmentation pattern with major peaks at *m/e* 138 and *m/e* = 124.

Various combinations of reaction time and temperature were exhaustively investigated in attempts to improve the yields (10–20%) of this cleavage reaction. Reactions were carried out both in digol at atmospheric pressure and in alcoholic solvents in sealed tubes at various temperatures. At temperatures above 200° appreciable decomposition was observed to occur with the formation of many by-products. The best conditions found were to use a 4-fold excess of potassium cyanide in digol and heat the solution at 200° under nitrogen for 3–4 hr. Blank experiments conducted using the quaternary salt **3** alone under these conditions showed that the salt decomposed at these temperatures. This may explain the difficulties encountered in this cleavage reaction. The yields of the desired cyano compound **4** in sealed tube experiments using ethanol or methanol as the solvent were unpredictable and generally much lower than the corresponding reactions in digol.

Methanolysis of 16-cyanodihydrocleavamine to 16-methoxycarbonyldihydrocleavamine was initially attempted in refluxing methanolic hydrogen chloride. This however gave (±)-α-and-β-dihydrocleavamines, indicating that hydrolysis and decarboxylation tends to occur readily under these conditions. Under milder conditions, it was possible to obtain the four possible diastereoisomers methoxycarbonyldihydrocleavamine which easily separable by preparative chromatog and identifiable by mass spectrometry. One of possessed the same *Rf* value in several systems as an authentic sample† and an ide mass spectrum. High resolution mass spectro on the molecular ion confirmed the molecular mula as $C_{22}H_{28}N_2O_2$. The mass spectra of diastereoisomeric 16-methoxycarbonyldihydroc amines obtained by reaction of catharanthine zinc in glacial acetic acid have already been lished.[16]

The formation of (±)-16-cyanodihydroc amine by cleavage of the C—$N^{(+)}$ bond cyanide anion in a hexahydropyrrocoline sy with the consequent generation of nine memb ring provides a novel reaction of its kind. It ma of fairly general use and after the publication preliminary communication of this work[17] K *et al.* have applied it in the synthesis of vinca mine[18] and 16-methoxycarbonyldihydro amine.[19] Inspite of the rather low yields cyanide cleavage reaction, this synthesis of methoxycarbonyldihydrocleavamine represent overall improvement in yields over the synthesis[14] by a factor of 10^3.

The mercuric acetate oxidation of methoxycarbonyldihydrocleavamine affords Iboga alkaloids coronaridine and dihydrocath thine.[29,30] Since the conversion of these compo to ibogamine, epi-ibogamine[20] and catharan are known the synthesis described here fo constitutes a synthesis of these alkaloids also.

It had been generally accepted that cleava like tetracyclic indoles are the biogenetic prec to vinblastine and vincristine. Inspite of inte investigation of *Catharanthus roseus*, no such racyclic indoles have been isolated. This led us (A. R.) to propose a novel biogenetic hypot by which such binary alkaloids could arise by direct attack of vindoline on an Iboga such as catharanthine[22,23] or its derivative. first demonstration of such a semi-synthetic ach based on the use of catharanthine and ine led to the synthesis of 16-epi-rovinblastine.[22] This hypothesis has been ver-[31] by labelling experiments and has re- in dramatic advances in the syntheses of alkaloids during the last few years, all based this biosynthetic approach[25–27].

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† Kindly supplied by Professor George Büchi of M U.S.A.

EXPERIMENTAL

IR spectra were recorded on Unicam SP-200 or -Elmer 137 spectrophotometer. The UV spectra recorded in 95% EtOH on a Cary model 145 M–50 photometer or on a Perkin–Elmer model 137 UV . NMR spectra were recorded on Varian XL NMR spectrometer. Mass Spectra were recorded A.E.I. MS-9 spectrometer. Column chromatog-y was carried out using Woelm activity III alumina. carried out on silica gel GF-254 plates. Glc was out on Perkin–Elmer F-11 gas chromatographs or M model 720 dual column gas chromatograph. M ps determined microscopically with Kofler block. All are uncorrected.

Ethyl *dimethyl malonate.* Na wire (138.0 g atom) placed in a 5-litre flask and super-dry MeOH (1.3 from magnesium methoxide) distilled directly into action flask, the temp being carefully controlled by bath. The solon was refluxed till all the Na had ved. Distilled dimethyl malonate (790.0 g, 6.0 mole) added and the solon heated to gentle boiling with . The sodio derivative of dimethyl malonate was . EtI (1200 g, 7.6 mole) was added dropwise and dio derivative was observed to dissolve slowly. The was allowed to stand overnight.

clear supernatant liquid was decanted off from the deposit of NaI. The solid was washed with MeOH the washings added to the decanted solon. The OH was evaporated under vacuum and the residual liquid added to about 4 litres of distilled water. base was neutralised with 3% HCl and the solon ted with ether. The ether extracts were shaken with S_2O_3al, dried over $MgSO_4$ and the ether evaporated under vacuum. The residual liquid was distilled (190°–760 mm.) to afford 2-ethyl dimethylmalonate (190 g, yield). IR spectrum: ν max 1750 cm^{-1} (C=O).

Methyl-2-*carboxybutanoate.* To 2-ethyl dimethyl (790 g, 4.9 mole) was added dry MeOH (1.5 l.) the solon cooled to 0° with an acetone-solid CO_2 KOH (Analar, 330 g) was separately dissolved in drous MeOH (2 l.) and the methanolic solon of KOH cooled to 0°. The cold alkaline solon was then added ise to the stirred malonate solon over 30 min. The was allowed to stand at 0° for 4 hr. The MeOH was evaporated off to leave a white crystalline mass. This dissolved in distilled water (2 l.) and the solon fied with 3N HCl till no more oily droplets sepa-. The solon was ether-extracted, the ether extracts and evaporated to afford a colourless viscous liquid g, yield = 97%) IR spectrum: ν max 3520 cm^{-1} (free- 1750 cm^{-1} (C=0, ester), 1715 cm^{-1} (C=O, acid).

Methyl-2-*ethyl acrylate* (4). Methyl-2-carboxybutan- (700 g, 4.8 mole) was cooled in an acetone-solid CO_2 10°. Diethylamine (400 g, 5.5 mole) was added e to the cold stirred solon over a period of 3 hr. formalin solon (740 g,) was added and the mixture for 2 days. K_2CO_3 (75 g) in distilled water (400 l) was then added and the solon extracted with ether. ether extracts were dried over $CaCl_2$ and the ether lly distilled to afford methyl-2-ethyl acrylate (540 g, yield = 78%). IR spectrum: ν max 1625 cm^{-1} (C=C), 1715 cm^{-1} (C=O), 3000 cm^{-1} (C=H). NMR ($CDCl_3$): δ 1.04 (triplet), δ 2.32 (quadruplet), δ 3.7 (singlet), δ 5.50 (singlet), δ 6.08 (singlet).

(4) *Preparation of ethyl*-2-*carbethoxy*-4, 4-*diethoxybutanoate* (3). Na (80 g, 2.5 g atom) was dissolved in anhyd EtOH (1.0 litre, from magnesium ethoxide). Distilled diethyl malonate (560 g, 3.5 mole) was added to the hot solon. Most of the EtOH was evaporated off and then distilled anhyd DMF (1.0 l.) added. The azeotropic mixture was distilled till the reflux temp reached 120°. Bromoacetal (446 g, 2.26 mole) was then carefully added dropwise. The solon was refluxed (120°) for 4 hr and allowed to cool overnight. The solon was then poured into ice cold water (2 l.) and extracted into ether. The ether extracts were successively washed with cold salt solon, $Na_2S_2O_3$al and distilled water. The ether extracts were dried over $NaSO_4$ and evaporated to a reddish liquid. Distillation (155°–157°, 13–14 mm) afforded the desired product **3**. (450 g, 72% yield).

(5) *Preparation of methyl*-2-*ethyl*-4, 4-*dicarbethoxy*-6, 6-*diethoxy-hexanoate* (5). Na (5.0 g, 0.215 g atom) was dissolved in anhyd EtOH (150 ml) by stirring at room temp. Ethyl-2-carbethoxy-4, 4-diethoxy butanoate (140 g, 0.54 mole) was then added and the solon observed to turn yellowish as the Na salt formed. Methyl-2-ethyl acrylate (58.9 g, 0.51 mole) was added dropwise over 30 min and the solon stirred magnetically at room temp for 72 hr. The solon was observed to have developed a brownish-red colour by the end of this period. The reaction flask was kept under N_2 throughout the course of this reaction. The brownish-red liquid was poured into cold dil NH_4Clal and extracted with ether. The ether extracts were dried (Na_2SO_4) and evaporated and the residual viscous liquid distilled (140°–141°, 0.3 mm) to afford the desired product (180 g, yield = 86%). IR spectrum: ν max 1700–1730^{-1} broad (C=0); (Found; C, 58.8 H, 8.96. Calc: C, 58.5 H, 8.74.)

(6) *Preparation of* 2 (2′-*methoxycarbonyl butane*)-2-*carbethoxy*-3-*oxo*-1,2,3,5,6, 11*b*-*hexahydro*-11*h*-*indolo*-(3, 2-g)-*pyrrocoline*-(**7**) Compound **5** (34.7 g, 0.07 mole) and tryptamine (14.63 g, 0.093 mole) were dissolved in glacial AcOH (265 ml) containing distilled water (90 ml). O_2-free nitrogen, (after passing through conc H_2SO_4 and solid KOH traps) was bubbled through, and the solon gradually turned brownish-red. The solon was cooled and evaporated on a rotary evaporator to a high viscous reddish brown gum. This was dissolved in $CHCl_3$, and extracted with dil NaOHag (500 ml, 2.5 N solon). The $CHCl_3$ extracts were dried over Na_2SO_4 and evaporated to a reddish gum (37.5 gm). Attempted purification by column chromatography afforded a pale yellow gum which failed to crystallise.

A positive test for a β-carboline was observed: compound (0.005 g.) + conc H_2SO_4 (2 drops) + $FeCl_3$ (0.005 g). bluish-black colouration.

IR spectrum: ν max 3270 cm^{-1} (N−H), 1675 cm^{-1} (C=O, lactam), 1722 cm^{-1} (C=O, ester); UV spectrum: λ max: 220, 264, 290 nm., ε max: 37500, 6730, 6730, 5100; λ min: 246, 267, 288 nm. ε min 2920, 6610, 4990.

(7) *Preparation of* 2(2′-*carboxy butane*)-2-*carboxy*-3-*oxo*-1,2,3,5,6, 11*b*-*hexahydro*-11*h*-*indolo*-3,2-*g*-*pyrrocoline* (**8**). Compound **7** (118.0 g, 0.286 mole) was dissolved in 10% methanolic KOH solon (1.0 l.) and distilled water (0.5 l.) added. The solon was refluxed for 30 min under N_2. The solon was then cooled and evaporated to a reddish brown gum. This was diluted with water and charcoaled with activated charcoal (3.0 g). The filtrate on acidification with moderately conc HCl afforded a yellow solid ppt. The solon was allowed to stand overnight at 0° and the aqueous mother liquors decanted off. The residual solid was washed twice with dil HCl and once with distilled water. The solid was then dried in an air stream

to afford the crude yellowish solid product (100.0 g, crude yield = 95%). Column chromatography using activity II alumina with 1.0 g of the substance resulted in the diacid becoming strongly adsorbed on the column.

When the crude product was ground with a small quantity of $CHCl_3$ or allowed to stand in a minimum quantity of $CHCl_3$ at 10°, it slowly crystallised out as colourless crystals (m.p. 273–274°). IR spectrum: ν max 3320 cm^{-1}(indole N–H); 1670 cm^{-1} (lactam C=O); 1725 cm^{-1} (acid C=O); UV spectrum: λ max 223, 272, 231, 290$_n$m; ε max 32800, 6240, 5680; λ min 248, 277, 288nm; ε min 3090, 6130, 5160. (Found:C, 64.79, H, 5.88 N, 7.23%. Calc: C, 64.9, H, 5.94, N, 7.56%.)

(8) *Preparation of* 2(2′-*carboxy butane*)-3-*oxo*-1,2,3,5,6, 11*b*-*hexahydro* 11*h*-*indolo*-(3, 2-*q*)-*pyrrocoline* (**9**). The acid **8** (100 g, 0.27 mole) was intimately ground with an equal weight of copper-bronze powder. The flask was evacuated to 0.15 mm pressure and heated on an oil bath at 170° for 3 hr. After cooling, the solidified mass was scraped out, finely ground in a mortar and dissolved in dil NaOHaI to give a dark coloured solon. Charcoaling and filtration produced little improvement in colour. The solon was acidified with dil HCl when a yellowish brown solid precipitated out. This was dissolved in $CHCl_3$, the $CHCl_3$ layer dried ($MgSO_4$) and evaporated to a yellow amorphous froth (83.0 g). Column chromatography using activity III Woelm neutral alumina or silicic acid afforded pale-coloured eluates. The gum obtained from these eluates was crystallised from MeOH as pale-yellow needles (m.p. 219–220°). IR spectrum: ν max 1665 cm^{-1} (C=O, lactam), 1725 cm^{-1} (C=O, acid); U.V. spectrum λ max 223, 281, 298, nm; ε max 33400, 6690, 15570, λ min 248, 287 nm; ε min 3820, 5190; (Found: C, 73.3, H, 8.0, N, 8.9%; Calc: C, 73.1, H, 7.7, N, 8.97%), mass spectrum: m/e = 326 (M^+, 100%), 325 (40%), 280 (15%), 279 (12%), 264 (5%), 237 (15%), 225 (221%), 224 (65%), 223 (14%), 211 (23%), 196 (9%), 171 (11%), 170 (10%), 169 (23%), 168 (13%), 167 (13%), 156 (9%), 154 (7%), 144 (10%); high resolution mass spectrometry: calculated: M^+ = 326.163032, observed: M^+ = 326.166475.

(9) *Preparation* 2(2′-*methoxycarbonl butane*)-3-*oxo*-1,2, 3,5-11*b*-*hexahydro*-11-*h*-*indolo*-(3, 2-*g*)-*pyrrocoline* (**10**). The crude acid **9** (85.0 g, 0.26 mole) was dissolved in anhyd MeOH (1 l.). BF_3-MeOH complex (200 ml) was added and the solon refluxed under N_2 for 2½hr. After cooling, it was evaporated to a viscous liquid and poured into ice cold water (2.0 l.). The brown ppt was dissolved in ether and extracted with 10% NaOHaI. The ether extracts were dried and evaporated to a viscous liquid. On addition of benzene and scratching of the sides of the flask, crystallisation began. Repeated crystallisations afforded 30.0 g of crystalline material (m.p. = 71°).

Overall yield starting from 118 g of **7** = 30% IR spectrum: ν max: 1660 cm^{-1} (lactam C=O), 1725 cm^{-1} (ester C=O); UV spectrum: λ max: 222, 273, 281, 290 nm; ε max: 38800, 7300, 7510. 6150; λ min 248, 274, 288nm; ε min 3400 7250, 5740; (Found: C, 70.57, H, 7.21; N, 8.44%; Calc for: C, 70.58; H, 7.05, N, 8.23%), NMR spectrum: δ 7.1–7.8 multiplet (4H, aromatic protons) δ 3.66 singlet (3H, ester methyl).

(10) *Alternative preparation of* 2(2′-*methoxycarbonyl-butane*)-3-*oxo*-1,2,3,5,6 11*b*-*hexahydro*-11-*h*-*indole*-(3, 2-*g*)-*pyrrocoline* (10) *via methyl*-2-*ethyl*-4-*carbethoxy*-6, 6-*diethoxyhexanoate* (**6**). Compound **5** (9.8 g, 0.0256 mole) was added to anhyd dimethyl sulphoxide (100 ml). Dry sodium cyanide (2.0 g, 0.04 mole) was added. The solon was magnetically stirred and heated under N_2 at 160° for 4–5 hr. Aliquots were drawn continuously and the reaction followed by glc. At the end of this period, 95% of the starting material was observed to be converted to a more volatile product. The mixture was cooled and poured into cold petroleum ether (60°–80°). The petroleum ether extracts were dried (Na_2SO_4) and rated to afford **6** as a colourless liquid (5.8 g, 73%

Compound **6** (4.7 g, 0.015 mole) was added to a of tryptamine (2.6 g, 0.016 mole) in 60% aqueous AcOH (50 ml). The solon was magnetically stirred refluxed under N_2 for 6 hours. It was cooled night and evaporated to a viscous liquid on the evaporator. The gum was taken up in $CHCl_3$ (100 extracted first with 2N NaOH (100 ml) then with 2 (100 ml). The $CHCl_3$ extracts were dried (Na_2SO_4) evaporated to a reddish gum. This was dissolved in zene and rapidly filtered through activity II Woelm alumina when colour was observed to stay and a colourless filterate was obtained Evaportion of benzene solution afforded a gum which could be crystallised to afford colourless crystals (m.p. 71°, yield = 85%.

The product obtained was found to be identical in respects with **10** prepared as described earlier.

(11) *Preparation of* 2(2′-*hydroxymethyl butane*)-1,2,3 11*b*-*hexahydro*-11-*h*-*indolo*-(3, 2-g)-*pyrrocoline* (11). lactam **10** (24 g, 0.07 mole) was dissolved in anhyd (500 m.) Fresh LAH (17 g) was carefully added to magnetically stirred solon. The solon was refluxed for cooled and the excess of LAH carefully destroyed drops of water. The solon was shaken with a satu solution of Rochelle salt (500 gm) to dissolve and the Li and Al salts. The aqueous solon was then extr with ether, the ether extracts dried (Na_2SO_4) and eva rated to a white froth (18.5 gm., yield = 90%). Ca column chromatography over activity III alum (Woelm, neutral) as well as over silicic acid also yie no crystals. Attempted picrate, methopicrate, hydroc loride, hydrobromide, methiodide, tartrate and oxa formations failed to yield any crystalline derivatives. substance could be sublimed at 10^{-4} mm. pressure to a colourless non-crystalline glass (m.p. = 72–74°, able). IR spectrum: ν max: 3620 cm^{-1} (broad, O stretching, free), 1033 cm^{-1} (broad, O-H deform UV spectrum: λ max: 225, 265, 292, 300 nm; ε 24210, 5100, 5400, 4900; λ min: 248, 260, 296 min: 3870, 5000, 4780; mass spectrum: m/e 298 (73%), 297 (100%), 211 (17%), 209 (18%), 184 (65 183 (15%), 170 (19%), 169 (18%), 168 (14%), (28%), 144 (16%), 143 (10%), 135 (11%), high resolu tion mass spectrum: calcd for $C_{19}H_{26}N_2O$ = 298. obtained for M^+ = 298.200.

(12) *Preparation of the quaternary salt* (**12**). The alc **11** (0.915 g, 0.00307 mole) was dissolved in anhyd eth Triethylamine (0.322 g, 0.00318 mole) was added volume with a syringe. Then redistilled methane phonyl chloride (0.385 g, 0.00337 mole) was added to magnetically stirred solon. Immediately a product st to precipitate out. The solon was allowed to stir under for 13 hr. The ethereal solon was then decanted and residual solid washed twice with ether. It was then dis ved in water (20 ml). On basification with dil NaOHaI, immediate precipitation of the free bases (amino alc and the corresponding mesylate (which had been pre as water-soluble compounds in the form of their hyd lorides) occurred. The ppts were extracted into CH_2Cl_2 and evaporated to give a yellow solid (0.847 which was shown by tlc to be a mixture of some unrea **11** and the newly formed mesylate. The mixture ga positive test for sulphur.

The products obtained above were dissolved refluxed in acetonitrile for 9 hrs till tlc showed that spot corresponding to the mesylate had completely dis peared. The acetonitrile was evaporated off and the maining solid taken up in water and CH_2Cl_2. The wa soluble material was exhaustively extracted with succ sive portions (50 ml) of benzene, CH_2Cl_2 and EtOAc completely remove and recover any unreacted **11**. Wh wed that no more amine alcohol was present but a polar compound (base spot corresponding to the ary salt), the aqueous layer was separated and ated to a pale yellow solid. Yields based on unre- amine alcohol were up to 90%. The recovered alcohol was recycled back into the same reaction. tography of the quaternary salt over a cellulose still afforded an amorphous product. UV spec- λ max: 222, 268, 293nm; λ min: 267, 243nm; IR : Absorption for O-H, lactam C = O, ester C = O C = O absent.

Preparation of α-and β-dihydrocleavamines (**13**) *and* (b) To the quaternary salt **12** (1.2 g, 0.00319 mole) stilled in liquid ammonia (23 ml). The solon was in an acetone-solid CO_2 bath. Little chips of Na added and the colour maintained blue for 1 hr. The was then extinguished by the addition of a little O and the ammonia allowed to evaporate at room EtOAc (20 ml) and distilled water (20 ml) were added and the aqueous solon thoroughly extracted EtOAc. The organic layer was separated, dried SO_4) and evaporated to afford the product (0.66 g, = 72%). Comparison of this synthetic product with tic α-and β-dihydrocleavamine on tlc in several systems (92% $CHCl_3$-8% MeOH, or 100% Ac etc) showed that the two spots which appeared on besides a faint base spot) had identical Rf values as ydrocleavamine and β-dihydrocleavamine respec- Both compounds were found to be indolic by UV copy.

Careful separation of the two spots by preparative tlc mass spectral determination of each of the spots that they were identical to the authentic samples. mass spectra were found to be completely superim- ble on those of the authentic dihydrocleavamines; spectrum: $m/e = 282$ (7%), 156 (4%), 145 (6%), (100%), 124 (10%); high resolution mass spec- try: calculated for $C_{19}H_{26}N_2O = 282.209589$, ob- $m/e = 282.209589$; analysis: sublimed under high several times and submitted for analysis: Found: C, 79.73, H, 9.52%. Calculated C, 80.85, H, %.)

The salt **12** (0.200 g, 0.00053 mole) was dissolved in N-methylmorpholine. LAH (0.35 g) was added and solon refluxed for 15 hr. The solon was cooled and LAH carefully destroyed by addition of drops of After addition of Rochelle salt solon, the aqueous was exhaustively extracted into EtOAc. The EtOAc was separated dried ($NaSO_4$) and evaporated to β-dihydrocleavamines (0.13 g, yield = 86%).

Preparation of 16-cyanodihydrocleavamine (**17**). (a) salt **12** (0.200 g, 0.0053 mole) was dissolved in anhyd OH (5 ml). KCN (Analar quality, 0.12 g) was added to solon of the quaternary salt in a tube and the tube under N_2. The sealed tube was heated in a rocking at 220°–240° for 3 hr. The furnace was then to cool over 4 hr. The sealed tube was opened the brown methanolic solon diluted with water when ppt appeared. The mixture was evaporated under to remove all the MeOH and the aqueous solon extracted with EtOAc (20 ml). The EtOAc extracts dried (Na_2SO_4) and evaporated to a gum (0.167 g). showed that this was a complex mixture. Individual ents were separated by preparative tlc and a running spot observed to bear a C≡N grouping by ation of its IR spectrum. This was isolated by the silica gel powder obtained from the corres- region of the plate with EtOAc. The EtOAc were combined and filtered and the filtrates to afford a colourless gum which crystallised petroleum ether (60–80), yield of pure crystals = 8% = 185-190°).

The salt **12** (0.175 g, 0.00046 mole) was dissolved in anhyd digol (2 ml). KCN (1.5 g, 0.023 mole) was added and the mixture heated under N_2 for $2\frac{1}{2}$ hr at 190°. The solon was magnetically stirred during the reaction. A rapid darkening of the solon was observed. The dark brown liquid was poured into distilled water (25 ml) when a brown ppt appeared. This was dissolved in EtOAc and the aqueous solon extracted several times with EtOAc (50 ml). The organic extracts were separated, dried (Na_2SO_4) and evaporated to a gum (0.07 g). This was separated by preparative tlc and the faster-running **17** isolated and crystallised from petroleum ether 60°–80° (0.014 g, yield = 10%). IR spectrum: ν max 3330 cm^{-1} (-NH), 2240 cm^{-1} (C-H), 2805 cm^{-1} 2755 cm^{-1} (Bohlmann bands), UV spectrum: λ max 226, 284, 293nm, ε max 36800, 8830, 7700, ε min 248, 291nm, ε min 2590, 6850, λ inflection 278, ε inflection 8060; mass spectrum: $m/e = 307$ (53%, M^+), 182 (19%), 181 (16%), 168 (43%), 156 (10%), 155 (12%), 154 (15%), 144 (12%), 143 (12%), 140 (15%), 139 (21%), 138 (97%), 137 (10%), 130 (11%), 128 (12%), 127 (13%), 126 (100%), 125 (20%), 124 (60%), 100 (39%), (Found: C, 77.95, H, 7.96, 13.59%: Calc for: C, 78.17 H, 8.14; N, 13.68%.

Attempted preparation of 16-methoxycarbonyldihydrocleavamine (**18**)*-decarboxylation to α- and β-dihydrocleavamines.* Compound **17** (0.025 g) was dissolved in 1.5% methanolic HCl (5 ml) prepared by passing dry HCl gas into anhyd MeOH. The solon was refluxed in an atmosphere of N_2 for 18 hr. The dark methanolic solon was evaporated on a rotary evaporator and the residue was dissolved in water. When the aqueous solon was basified with $NaHCO_3$al, a pale yellow ppt came out of the solon. This was extracted with ether, the ether extract dried (Na_2SO_4) and evaporated to afford a gum (0.016 g). Tlc comparison indicated that the material prepared was not **18** but the decarboxylated α- and β-dihydrocleavamines. This was confirmed by mass spectrometeric examination since the mass spectrum of the product obtained was identical to that of authentic samples of α- and β-dihydrocleavamines.

(16) *Preparation of* (±)*-16-methoxycarbonyldihydrocleavamines* (**18**). Compound **17** (0.012 g) was dissolved in anhyd MeOH (2 ml, distilled from magnesium methoxide). Dry HCl gas was bubbled in for 2 min till a 1% acid solon was obtained. The solon was kept at room temp while dry HCl gas was being bubbled through by continuously immersing the flask in an ice-cold bath as required. The solon was allowed to stand at room temp for 18 hr. It was then evaporated to a whitish solid. The solid was dissolved in water and basified with $NaHCO_3$al when a white ppt came out of the solon. This was extracted into ether, dried and evaporated to afford a colourless gum (0.009 gm). Tlc comparison against an authentic sample of 16-methoxycarbonyldihydrocleavamine showed the presence of six different spots. The four major spots were found to have mass spectra similar to that of authentic 16-methoxycarbonyldihydrocleavamine. One of these three spots also had the same Rf. value as the authentic material supplied by Professor Buchi. High resolution mass spectrometry established the formula of the molecular ion as $C_{21}H_{28}N_2O_2$. Mass spectrum: (a) Authentic sample $m/e = 341$ (7%) 340 (29%, M^+), 325 (2%), 281 (5%), 254 (2%), 215 (4%), 211 (6%), 210 (36%), 209 (2%), 202 (2%), 198 (1%), 197 (1%), 196 (2%), 195 (1%), 194 (2%), 184 (1%), 183 (2%), 181 (2%), 180 (6%), 170 (8%), 169 (7%), 168 (5%), 167 (4%), 162 (2%), 157 (2%), 156 (6%), 155 (4%), 154 (6%), 140 (3%), 139 (13%), 138 (100%), 137 (13%), 136 (4%), 124 (18%), (b) Synthetic sample $m/e = 341$ (7%), 340 (31% M^+) 325 (2%), 281 (6%), 254 (3%), 215 (3%), 211 (6%), 210 (38%), 209 (2%), 202 (3%), 198 (1%), 197 (1%), 196 (2%), 195 (1%), 194 (3%), 184 (2%), 183 (3%), 182 (5%), 181 (3%), 180 (6%), 170

(8%), 169 (9%), 168 (7%), 167 (7%), 162 (1%), 157 (3%), 180 (6%), 170 (8%), 169 (9%), 168 (7%), 612 (1%), 157 (3%), 156 (8%), 155 (8%), 154 (8%), 154 (8%), 140 (3%), 139 (13%), *138 (100%)*, 137 (17%), 136 (3%), 124 (27%).

High resolution mass spectrum: calculated for $C_{21}H_{28}N_2O_2$: 340.215066; obtained for $m/e = 340$: 340.214115.

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